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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: A.G. Uitterlinden et al. Attorney Docket No.: KILS117128

Application No.: 09/786,991 Group Art Unit: 1634

Filed: March 9, 2001 Examiner: S.A. Sakelaris

Title: METHOD FOR DETERMINING THE SUSCEPTIBILITY TO BONE DAMAGE BY SCREENING POLYMORPHISMS IN THE VITAMIN D RECEPTOR

AMENDMENT A

Seattle, Washington 98101
August 26, 2002

TO THE COMMISSIONER FOR PATENTS:

In response to the Office Action mailed April 19, 2002 (Paper No. 8), applicants submit the following amendment to the above-identified patent application, together with the appended remarks.

In the Specification:

Please amend the paragraph beginning at page 12, line 15 as follows:

The present invention will now be described in detail with reference to the following examples and figures.

BRIEF DESCRIPTION OF THE DRAWINGS

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FIGURE 1 is a schematic presentation of the region between exon 7 and the 3' UTR of the vitamin D receptor genes.

Please amend the paragraph beginning at page 13, line 27, as follows:

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We then went on to determine the distribution of fractures in women according to their carrier status for VDR haplotype 1 (Table 3). Significantly more women heterozygous for VDR haplotype 1 had fractures than the women in the reference group and for women homozygous for the VDR haplotype 1 this difference further increased. When women were grouped according to

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VDR haplotype 2, we observed an under-representation in fracture cases (p=0.002) while for VDR haplotype 3 no differences were observed (p=0.65; data not shown). Logistic regression analysis showed that women heterozygous for the VDR haplotype 1 had 1.8 times the risk for fractures compared to women in the reference group. This was further increased for women homozygous for the VDR haplotype 1 to 2.6 times the risk for fracture compared to women in the reference group (Table 3). When we analyzed by type of fracture we observed the VDR genotype effect to be similar for vertebral fracture cases (p=0.07) and non-vertebral fracture cases (p=0.04; data not shown). The relative risk of fracture did not essentially change after adjustment for potential confounding factors such as age, weight, and bone density in the multivariate regression analysis.

Please amend the paragraph beginning on page 14, line 15, to read as follows:

In this group of women we also determined the distribution of fractures according to COLIA1 genotype (Table 3). In correspondence with what we previously found[10] we observed the COLIA1 T allele to be associated with increased fracture risk, independent of BMD. To assess whether there was interaction between the VDR haplotype effect and the COLIA1 genotype effect on fracture we determined the distribution of fractures according to VDR haplotype 1 in the different COLIA1 genotype groups (Table 4). The distribution of fracture cases according to the VDR genotype did not differ in the group of women with the COLIA1 GG genotype. However, in the COLIA1 risk groups of women with the GT and TT genotypes the distribution of fractures cases was strongly VDR genotype dependent (Table 4). Logistic regression analysis showed that the effect of VDR genotype on fracture risk is absent in women with the COLIA1 GG genotype while the VDR genotype effect is large in the COLIA1 hetereozygous GT and homozygous TT risk group (Table 4). When age, VDR genotype, COLIA1 genotype and fracture were considered together in a multivariate regression model we

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found that VDR genotype significantly modified the COLIA1 genotype effect (p=0.03 for the interaction term). The effect was found to be similar for nonvertebral fracture cases and vertebral fracture cases and when bone density was entered into the model the results did not change indicating the interaction effect to be independent of bone density.

Please amend the specification by inserting the following Tables 1-4 on page 18 prior to the claims.

TABLE 1

Number of postmenopausal women with fractures according to VDR Genotype

VDR Genotype	**No. with fracture / total No. (%)**
11	34 / 255 (13.3)
12	35 / 375 (9.3)
13	13 / 101 (12.9)
22	7 / 179 (3.9)
23	6 / 82 (7.3)
33	2 / 12 (16.7)
Chi2	13.3
P Value	0.04

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TABLE 2

Characteristics of 1004 postmenopausal women according to their VDR haplotype 1 genotype

Characteristic*	VDR genotype+			P Value
	Reference (n=273)	Heterozygotes (n=476)	Homozygotes (n=255)	
Age (yr)	66.4 ± 7.0	67.4 ± 7.0	67.1 ± 6.7	0.19
Height (cM)	162.3 ± 6.3	162.1 ± 6.0	161.7 ± 7.5	0.66
Weight (Kg)	68.9 ± 9.7	68.6 ± 10.5	69.3 ± 10.5	0.70
Age at Menopause (yr)	49 ± 5	49 ± 5	49 ± 5	0.35
Dietary calcium intake (mg / day)	1076 ± 335	1103 ± 329	1073 ± 287	0.42
Current smoker (%)	20	21	24	0.51
Femoral Neck Bone Mineral Density (g / cm^2)	0.82 ± 0.15	0.80 ± 0.12	0.81 ± 0.13	0.21

* Plus-minus values are means ± SD

+ "Reference" includes VDR genotypes 22, 23, 33; "Heterozygotes" includes 12, 13; "Homozygotes" includes 11

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TABLE 3

Number of postmenopausal women with fractures and Odds Ratio for fracture according to VDR halotype 1 genotype and according to COLIA1 genotype

Genotype+	Fracture	Odds Ratio (95% Cl)	
	No. with fracture / total No. (%)	Age-adjusted	Multivariate*
a.	**By VDR haplotype 1 genotype**		
Reference	15 / 273 (5.5)	1.0	1.0
Heterozygotes	48 / 476 (10.1)	1.8 (1.0-3.3)	1.6 (0.8-3.1)
Homozygotes	34 / 255 (13.3)	2.6 (1.4-5.0)	2.4 (1.2-4.8)
Chi2	9.47	--	--
P Value	0.009		
b.	**By COLIA1 genotype**		
GG	53 / 679 (7.8)	1.0	1.0
GT	37 / 293 (12.6)	1.7 (1.1-2.7)	1.6 (1.0-2.6)
TT	7 / 32 (21.9)	3.7 (1.5-9.2)	3.3 (1.3-8.4)
Chi2	11.1	--	--
P Value	0.004		

+ "Reference" includes VDR genotypes 22, 23, 33; "Heterozygotes" including 12, 13; "Homozygotes" including 11

* Multivariate Odds Ratios were adjusted for age, weight, and femoral neck BMD.

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TABLE 4

Number of postmenopausal women with fractures and Odds Ratios for fractures according to combined VDR haplotype 1 and COLIA1 genotype

VDR genotype*	COLIA1 genotype			
	GG	GT	TT	GT + TT
a.	*Number with Fractures / total number (%)*			
Reference	13 / 194 (6.7)	2 / 70 (2.9)	0 / 9 (0)	2 / 79 (2.5)
Heterozygotes	27 / 315 (8.6)	18 / 149 (12.1)	3 / 12 (25.0)	21 / 161 (13.0)
Homozygotes	13 / 170 (7.6)	17 / 74 (23.0)	4 / 11 (36.4)	21 / 85 (24.7)
Chi2	0.59	13.3	3.94	17.3
P Value	0.74	0.001	0.14	0.0002
b.	*Age-adjusted Odds Ratio (95% CI)**			
Reference	1.0	0.4 (0.1-2.0)	_¶	0.4 (0.1-1.8)
Heterozygotes	1.3 (0.6-2.5)	1.9 (0.9-4.1)	4.8 (1.1-21)	2.1 (1.0-4.4)
Homozygotes	1.2 (0.5-2.7)	4.1 (1.9-8.5)	7.1 (1.8-29)	4.4 (2.0-9.4)

+ "Reference" includes VDR genotypes 22, 23, 33; "Heterozygotes" includes 12, 13; "Homozygotes" includes 11

* Odds Ratios were calculated with women with both the VDR haplotype 1 reference genotype and the COLIA1 GG genotype as reference group. Based on the small numbers of the COLIA1 TT genotype group and the similar trends we observed for the COLIA1 GT and the COLIA1 TT genotype groups, we calculated Odds Ratios for the combined COLIA1 GT+TT genotype group.

¶ Zero cases in the cell precluded the calculation of the Odds Ratio in the COLIA1 TT genotype group.

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Please delete Tables 1-4 that are currently set forth on the four pages (identified as 1/5, 2/5, 3/5, and 4/5) beginning after page 26.

In the Claims:

Please cancel claims 7 and 20; and amend claims 1-4, 6, 8, 13, 18, 19, 22-25, and 27-30 as shown below:

1. (Amended) A method of determining susceptibility to bone fracture in a subject, said method comprising analyzing genetic material of a subject to determine which of the B/b, A/a and T/t alleles of the *BsmI*, *ApaI* and *TaqI* sites of the vitamin D receptor gene are present, wherein the presence of a haplotype comprising at least one of the b, a and T alleles is indicative of an increased susceptibility to bone fracture.

2. (Amended) A method of determining susceptibility to bone fracture according to claim 1, said method comprising analysing genetic material of a subject to determine the presence of the baT haplotype of the vitamin D receptor gene, wherein the presence of said baT haplotype is indicative of an increased susceptibility to bone fracture.

3. (Amended) A method of determining susceptibility to bone fracture according to claim 1 or claim 2, said method further comprising analysing the genetic material of a subject to determine whether an allele of the collagen Iα1 gene is present which is indicative of an increased susceptibility to bone fracture.

4. (Amended) A method of determining susceptibility to bone fracture according to claim 3, said method comprising determining the presence of a G to T polymorphism at the *Sp*1 site of the collagen Iα1 gene, wherein detection of said polymorphism is indicative of an increased susceptibility to bone fracture.

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6. (Twice Amended) A method of determining susceptibility to bone fracture according to claim 3, said method further comprising determining the copy number of the B/b, A/a or T/t alleles of the vitamin D receptor gene and/or the S/s allele of the collagen Iα1 gene.

8. (Amended) A method according to claim 6 comprising comparing the allele(s) present in the genetic material of the subject with genotypes of the vitamin D receptor or collagen Iα1 genes having known degrees of risk of bone fracture.

9. A method according to claim 3, further comprising determining calcium levels in a subject.

10. A method according to claim 9 wherein daily calcium intake is measured.

11. A method according to claim 1, wherein said method is performed *in vitro*.

12. A method according to claim 11, wherein said method is performed on blood, or tissue samples of a subject.

13. (Twice Amended) A method of treating a subject to reduce the risk of bone fracture comprising analysing genetic material of a subject to determine which of the B/b, A/a and T/t alleles of the *BsmI*, *ApaI* and *TaqI* sites of the vitamin D receptor gene are present, wherein the presence of a haplotype comprising at least one of the b, a and T alleles is indicative of an increased susceptibility to bone fracture, and treating the subject to reduce the risk of bone fracture if the subject has a haplotype comprising at least one of the b, a and T alleles.

14. A method according to claim 13, wherein suitable treatments include modifications to lifestyle, regular exercise, changes in diet or pharmaceutical preparations.

15. A method according to claim 1, wherein the subject is a mammal.

16. A method according to claim 15, wherein the subject is a human.

17. A method according to claim 15 or 16, wherein the subject is a female.

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18. (Amended) A method of formulating a treatment regimen to decrease the risk of bone fracture, said method comprising analysing genetic material of a subject to determine the presence of the baT haplotype of the vitamin D receptor gene, wherein said haplotype is associated with risk of bone fracture, and formulating a treatment regimen to decrease the risk of bone fracture based on said haplotype.

19. (Amended) A method according to claim 18, further comprising determining which allele(s) of the collagen Iα1 gene is/are present.

21. A method according to claims 18 or 19 further comprising administering the appropriate treatment.

22. (Amended) A method of determining susceptibility to bone fracture in a subject comprising the step of utilizing a kit to determine whether the baT haplotype of the vitamin D receptor gene is present in a subject, wherein said kit comprises (i) one or more nucleic acid primer molecules for amplification of a portion of the vitamin D receptor gene, and (ii) means for determining whether the baT haplotype of said gene is present, and wherein presence of the baT haplotype in the subject is indicative of susceptibility to bone fracture.

23. (Amended) The method according to claim 22 further comprising the step of determining which allele of a collagen Iα1 gene is present in the subject, said kit further comprising (i) one or more nucleic acid primer molecules for amplification of a portion of the collagen Iα1 gene and (ii) means for determining which allele of the collagen Iα1 gene is present.

24. (Amended) A kit for determining susceptibility to bone fracture in a subject, said kit comprising (i) one or more nucleic acid primer molecules for amplification of a portion of the vitamin D receptor gene, (ii) means for determining whether the baT haplotype of said gene is present; and (iii) means for indicating correlation between the presence of said haplotype and risk of bone fracture.

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25. (Amended) A kit according to claim 24, said kit further comprising (i) one or more nucleic acid primer molecules for amplification of a portion of the collagen Iα1 gene and (ii) means for determining which allele of the collagen Iα1 gene is present.

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26. A kit according to claim 24 or claim 25, said kit comprising DNA control samples, for comparison with DNA sequences of a subject.

27. (Amended) A method according to claim 1, wherein the haplotype is determined by amplification of a portion of the vitamin D receptor gene between exon 7 and the 3' UTR, followed by restriction enzyme digestion; or any other technique suitable for determining the genotype of a subject.

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28. (Amended) A method according to claim 2, wherein the haplotype is determined by amplification of a portion of the vitamin D receptor gene between exon 7 and the 3' UTR, followed by restriction enzyme digestion; or any other technique suitable for determining the genotype of a subject.

29. (Amended) A method according to claim 3, wherein the haplotype is determined by amplification of a portion of the vitamin D receptor gene between exon 7 and the 3' UTR, or amplification of the first intron of the collagen Iα1 gene, followed by restriction enzyme digestion; or any other technique suitable for determining the genotype of a subject.

30. (Amended) A method according to claim 4, wherein the haplotype is determined by amplification of a portion of the vitamin D receptor gene between exon 7 and the 3' UTR, or amplification of the first intron of the collagen Iα1 gene, followed by restriction enzyme digestion; or any other technique suitable for determining the genotype of a subject.

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REMARKS

Claims 1-4 and 6-30 are pending in the application and have been examined. Claims 1-4 and 6-30 stand rejected. Claims 7 and 20 have been canceled. Claims 1-4, 6, 8, 13, 18, 19, 22-25, and 27-30 have been amended. No new matter has been added by these amendments. Reconsideration and allowance of Claims 1-4, 6, 8-19 and 21-30 in view of the above amendments and following remarks is respectfully requested.

Response to Objections to the Specification

The Examiner's objection to informalities in the specification are believed to be moot in view of the foregoing amendments to the specification and the following remarks.

A. Insertion of Tables 1-4 into the Specification

Tables 1-4 are located on the four unnumbered pages beginning after page 26 of the specification. By this amendment, Tables 1-4 have been cancelled from the four unnumbered pages beginning after page 26 of the specification, and have been inserted into the specification at page 18. FIGURE 1 has been amended to delete the recitation of "5/5" and a substitute sheet is provided herewith. No new matter has been added by these amendments.

B. Labeling of Tables

Applicants have amended the specification to clarify the numbering of the tables.

C. Brief Description of the Drawings

Applicants have amended the specification to include the title "BRIEF DESCRIPTION OF THE DRAWINGS."

D. Restriction Enzymes listed in the Specification

The Examiner has asserted that there are discrepancies concerning the restriction enzyme sites within the VDR gene and the claims, however, applicants find no such discrepancies. Applicants specifically refer to the restriction enzyme "ApaI" as a site of interest within the VDR

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gene, which has the recognition sequence "GGGCCC," and not to "ApoI" which has the recognition sequence "PuAATTPy." The enzyme "ApaI" is consistently recited throughout the specification, see for example page 3, line 26; page 4, line 7; page 8, line 26; page 10, line 4; page 11, line 16; page 18, line 3 and also in claim 2. Applicants submit there is no reference to the restriction enzyme "ApoI" in the specification, and therefore request removal of the Examiner's objection based on restriction enzyme discrepancies.

The Rejection of Claims 22 and 23 Under 35 U.S.C. § 101

The Examiner has rejected claims 22 and 23 under 35 U.S.C. § 101 because the claimed recitation of a use, without setting forth any steps involved in the process results in a claim which is not a proper process claim. Applicants have amended claims 22 and 23 to recite methods of use and therefore request the removal of this grounds of rejection.

The Rejection of Claims 3, 6-10, 19, 20, 23, 25-26 and 29 Under 35 U.S.C. § 112,

First Paragraph

The Examiner has rejected claims 3, 6-10, 19, 20, 23, 25-26 and 29 under 35 U.S.C. § 112, first paragraph due to lack of enablement. The Examiner states that the specification does not provide enablement for methods and kits for determining the susceptibility to bone fracture comprising detecting any allele of the collagen Iα1 gene. Applicants disagree with the Examiner's conclusion for the following reasons.

As an initial matter, applicants note that claim 6 recites, *inter alia*, determining the copy number of the S/s allele of the collagen Iα1 gene, which the Examiner acknowledges is enabled by the specification, therefore removal of claim 6 from this grounds of rejection is requested.

Applicants submit that in view of the teaching of the current invention that the Sp1 allele of the collagen Iα1 gene is associated with an increased risk of bone fracture, the identification of additional polymorphisms in the collagen Iα1 gene in linkage disequilibrium with the disclosed

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Sp1 allele, and/or the haplotype baT in the VDR gene, is enabled by the specification, and further would be routine to one skilled in the art, and would not require undue experimentation. Moreover, a patent need not teach, and preferably omits, what is well known in the art. MPEP Section 2164.01.

Applicants have identified an allele which is a T/G polymorphism at the Sp1 binding site in the first intron of the collagen Iα1 gene which is associated with an increased risk of bone fracture. General methods for identifying the presence of polymorphisms in genes are disclosed in the specification and these methods were also well known in the art at the time of the invention. See specification at page 7, lines 25-29 and page 8, lines 1-4, which discloses the representative options of sequencing, visualization of heteroduplex patterns in agarose gels, use of denaturing gels to detect polymorphic sites, and separation using single-strand conformation polymorphism (SSCP) analysis. The present invention further discloses that the correlation between increased fracture risk and VDR phenotype may be collagen Iα1 dependent. See specification at page 6, line 28-29 and Example 1. The specification also provides guidance with respect to how modifying the collagen Iα1 gene product likely results in bone fracture where it states "[v]itamin D dependent regulation of expression of bone-specific genes, such as osteocalcin, has been well documented and also includes regulation of the expression of the collagen type I 1 at the level of transcription. In RT-PCR experiments the Sp1 polymorphism has been shown to lead to differential binding affinity of the Sp1 transcription factor and also to genotype dependent COLIA1 mRNA expression levels." See specification at p15, lines 20-25.

Once an allele (such as Sp1) is associated with a phenotype (such as increased risk of bone fracture), the inheritance pattern of the allele can be compared to the inheritance pattern of other polymorphisms that have been identified in a gene of interest (such as the baT haplotype in VDR). If the observed frequencies of haplotypes in a population does not agree with haplotype

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frequencies predicted by multiplying together the frequency of individual alleles, there is a linkage disequilibrium, which implies an interallelic interaction. Exemplary methods for this type of analysis are discussed in Example 1 of the specification where a correlation is shown between the baT haplotype of VDR and the collagen Iα1 gene Sp1 polymorphism and the phenotype of increased fracture risk. Once such a linkage disequilibrium is established, it is routine in the art to determine if other polymorphisms are in linkage disquilibrium with the known allele. Therefore, applicants submit the specification does enable one skilled in the art to detect additional polymorphisms in the collagen gene and test for linkage disequilibrium with the known alleles of Sp1 and baT. Applicants respectfully request removal of this grounds of rejection.

The Rejection of Claims 1-30 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 1-4 and 6-30 as being indefinite. The Examiner's objections to these claims under 35 U.S.C. § 112, second paragraph are believed to be moot in view of the foregoing claim amendments and the following remarks.

A. The Rejection of Claims 22 and 23

The Examiner has rejected claims 22 and 23 for failing to set forth any steps involved in the method. Claims 22 and 23 have been amended to clarify the steps involved in the claimed method.

B. The Rejection of Claims 1-6, 7-17 and 27-30

The Examiner has rejected claims 1-6, 7-17 and 27-30 for failing to recite a final process step which agrees with the preamble. Claim 1, from which claims 2-12, 15-17 and 27-30 depend, has been amended to recite a final process step which agrees with the preamble.

C. The Rejection of Claims 2-4, 6-10, 13-14 and 28-30

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The Examiner has rejected claims 2-4, 6-10, 13-14 and 28-30 as being indefinite due to lack of further limitations from claim 1. Claim 2, from which claims 3-4, 6, 8-10 and 28-30 depend, has been amended to clarify that it is directed to a method of determining susceptibility to bone fracture.

D. The Rejection of Claim 13

The Examiner has rejected claim 13 as being indefinite for failing to recite a final process step that agrees with the preamble. Claim 13 has been amended to recite a method of treating a subject to reduce the risk of bone fracture. Support for this amendment can be found in the specification on page 6, lines 6-10 and on page 10, lines 6-17.

E. The Rejection of Claims 18-21

The Examiner has rejected claims 18-21 for failing to recite a final process step that agrees with the preamble. Claim 18, from which claims 19-21 depend, has been amended to recite a method of formulating a treatment regimen to decrease the risk of bone fracture. Support for this amendment can be found in the specification on page 4, line 13-17 and page 10, lines 6-28.

F. The Rejection of Claim 20

Claim 20 has been canceled.

G. The Rejection of Claim 21

The Examiner has rejected claim 21 for failing to recite a final process that agrees with the preamble. Claim 18, from which claim 21 depends, has been amended to recite "a method of formulating a treatment regimen to decrease the risk of bone fracture." Applicants submit that the final step recited in claim 21 of "administering the appropriate treatment" is in agreement with the preamble in claim 18 as amended.

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H. The Rejection of Claims 24, 25 and 26

The Examiner has rejected claims 24, 25 and 26 due to improper antecedent basis over the recitation of "said allele(s)." Claims 24 and 25 have been amended to correct antecedent basis.

I. The Rejection of Claims 25 and 26

The Examiner has rejected claims 25 and 26 over the recitation of "said gene" as lacking proper antecedent basis. Claim 25, from which claim 26 depends has been amended to correct antecedent basis.

J. The Rejection of Claims 27-30

The Examiner has rejected claims 27-30 as being indefinite due to the phrases "may be determined" and "relevant portion." Applicants have amended claims 27-30 to substitute the phrase "may be determined" with "is determined." In addition, applicants have amended claims 27-30 to remove the phrase "relevant portion." In claims 27-30 applicants have added the phrase "amplification of the portion of the vitamin D receptor gene between exon 7 and the 3' UTR." In claims 29-30, applicants have added the phrase "amplification of the portion of the vitamin D receptor gene between exon 7 and the 3' UTR, or amplification of the first intron of the collagen Iα1 gene." Support for these amendments is found in the specification on page 9, lines 6-27. Applicants respectfully request removal of these grounds for rejection.

The Rejection of Claims 18, 21 and 24 Under 35 U.S.C. § 102(e) as Being Anticipated by U.S. Patent No. 5,939,260 (Spector)

The Examiner has rejected claims 18, 21 and 24 under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,939,260, issued to Spector et al. Claim 18 has been amended to clarify that it is directed to a method of formulating a treatment regimen to decrease the risk of bone fracture based on the presence of the baT haplotype of the vitamin D receptor gene.

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Claim 24 has been amended to correct an informality related to antecedent basis, and is directed to a kit for determining susceptibility to bone fracture in a subject with means for detecting the presence of the baT haplotype, and a means for indicating correlation between said haplotype and risk of bone fracture. The baT haplotype recited in claims 18 and 24 is further defined in the specification at page 3, line 24-29 and page 4 lines 1-9, which states in relevant part "[t]hese alleles are denoted B/b, A/a and T/t for restriction enzyme sites *Bsm1*, *ApaI* and *TaqI* respectively...."

Anticipation requires that each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. MPEP § 2131. The Spector reference fails to anticipate the claimed invention because the reference fails to describe the use of the ApaI restriction enzyme to detect polymorphisms in the vitamin D receptor gene. Furthermore, the reference does not teach methods and compositions directed to determining the susceptibility of bone fracture.

The Examiner cites Spector as teaching a method for predicting the response of a subject to treatment by detecting the presence of the "baT" haplotype of the vitamin D receptor gene, wherein such individuals are more susceptible to osteoarthritis. Applicants submit the teachings of Spector do not anticipate the claimed invention because there is no teaching or suggestion in Spector that ApaI is useful for detecting the presence of alleles associated with the risk of bone fracture. In Spector, the restriction enzyme ApoI was used for detecting osteoarthritis, in contrast to the claimed invention which uses ApaI to detect a risk of bone fracture. The difference between the restriction enzymes ApaI (recognition site "GGGCCC") and ApoI (recognition site "PuAATTPy") is significant in that they have different DNA recognition sites and will produce different restriction fragment lengths. Moreover, in the present invention, the haplotype baT in the vitamin D receptor gene indicates an increased risk of bone fracture. In

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contrast, Spector teaches detection and treatment of osteoarthritis, a degenerative joint disease As stated in the Spector reference "[o]steoarthritis, or degenerative joint disease as it is also known is one of the most common types of arthritis. It is characterized by the breakdown of the joint's cartilage..." See Spector, col. 1, lines 16-18. The Spector reference teaches a number of suitable treatments for patients with suscepetibility to osteoarthritis such as to keep the joints flexible, surgery to prevent or control joint stress, the use of a medial collateral ligament brace, and dermatological preparations (see Spector, col 4, lines 58-59 and lines 64-66). In contrast, the present invention is directed to detecting susceptibility to bone fracture. Suitable treatments for susceptibility to bone fracture include modifications to lifestyle, regular exercise, changes in diet to strengthen bones, and hormone therapy such as anabolic steroids and hormone replacement therapy. See specification, page 10, lines 12-17. Therefore, claim 18, directed to a method of formulating a treatment regimen to decrease the risk of bone fracture based on the presence of the baT haplotype of the vitamin D receptor gene where "baT" refers to the Bsm1, ApaI and TaqI alleles of vitamin D receptor gene is not anticipated by the teachings of Spector.

With respect to claim 24, the Spector reference teaches a diagnostic composition that includes primers for amplifying ApoI polymorphisms and an indicator composition with means for correlating the vitamin D receptor gene polymorphisms with predisposition to osteoarthritis. In contrast, the claimed invention includes PCR primers for amplifying ApaI polymorphisms with means for correlating results to susceptibility to bone fracture.

Applicants submit that because the cited reference fails to disclose every limitation of the claimed invention, the reference is not anticipatory, and withdrawal of this grounds for rejection is respectfully requested.

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The Rejection of Claims 19, 21, 25 and 26 Under U.S.C. § 103(a)

Claims 19, 21, 25 and 26 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the Spector reference in view of Ralston. With respect to the Ralston reference, applicants assume the Examiner is referring to the publication in Nature Genetics Vol. 14, October 1996. Claims 19 and 21 depend from claim 18 , which has been amended. Claims 25 and 26 depend from claim 24. As stated in the foregoing remarks, with respect to Claims 18 and 24, Spector fails to teach the use of the restriction enzyme ApaI for detecting polymorphisms in the vitamin D receptor gene and fails to teach methods and compositions to detect an increased risk of bone fracture. In view of the foregoing remarks, applicants submit that the teachings of Spector fail to teach, remotely suggest, provide any motivation to make or otherwise render obvious the invention as claimed. The deficiencies of the teachings of the Spector reference noted above are not cured by the teachings of the Ralston reference. Withdrawal of this grounds for rejection is respectfully requested.

The Rejection of Claim 26 Under 35 U.S.C. § 103(a)

Claim 26 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Spector. Claim 26 depends from claim 24. In view of the foregoing remarks with respect to claim 24, the teachings of Spector fail to teach, remotely suggest, provide any motivation to make or otherwise render obvious the invention as claimed. Therefore, applicants respectfully request removal of this grounds of rejection.

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CONCLUSION

Applicants believe that Claims 1-4, 6, 8-19 and 21-30 are in condition for allowance. If any issues remain that may be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone applicant's attorney.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the U.S. Postal Service in a sealed envelope as first class mail with postage thereon fully prepaid and addressed to the Commissioner for Patents, Washington, D.C. 20231, on the below date.

Date: 8/21/02 

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